Development of a novel technology for precise, efficient, and safe genetic modification of stem cells

Grant Award Details

Development of a novel technology for precise, efficient, and safe genetic modification of stem cells

Grant Type: Tools and Technologies I

Grant Number: RT1-01103

Investigator:

Name:	Carlos Barbas
Institution:	Scripps Research Institute
Type:	PI

Human Stem Cell Use: Embryonic Stem Cell

Award Value: $1,138,548

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Grant Application Details

Application Title: Development of a novel technology for precise, efficient, and safe genetic modification of stem cells

Public Abstract: Stem cells are unique among cell types found in the human body: These cells are pluripotent; that is, they can develop into any of the more than 200 cell types in the human body. A major goal of stem cell research is to develop treatments for patients who suffer from devastating and currently incurable conditions such as AIDS, Alzheimer's, liver disease, diabetes, Parkinson's disease, muscular dystrophies, spinal cord injuries, and inborn errors of metabolism. These patients might be treated with gene-modified or gene-corrected patient-specific human embryonic stem cells (hESCs). In the hESCs used for treatment, the bad or defective gene must be either replaced or repaired with a good or effective gene. In some cases, it may be important that the patient's hESCs be provided with a disease-fighting gene. Here, the genes need to be placed in safe sites in the genome. For example, we might be able to treat AIDS patients using hESCs modified to contain a gene to make them resistant to the HIV-1 virus or patients with Alzheimer's disease might be treated with neural stem cells equipped with a new gene that fights the development of Alzheimer plaques throughout the brain. Unfortunately, the current state of the art in gene delivery does not allow scientists to insert genes safely at any given site in the genome. We also lack efficient techniques to readily repair defective genes by exchanging them with good genes. Such technologies will be key to realizing the full potential of embryonic stem cell therapy. We propose to develop revolutionary new tools to satisfy this need, and we believe that the application of these tools will significantly improve the likelihood that human disease will be treated with hESCs within the next decade. We will use protein engineering and applied molecular evolution to develop a new technology that will allow scientists to add new genes to hESCs in a safe and targeted approach that does not rely on the potentially dangerous use of viruses. We will demonstrate the potential of this approach by developing several hESC lines wherein we place specific reporter genes at defined sites in hESC genome. We will characterize the efficiency and accuracy of our approach and show that modified hESCs can be effectively differentiated to other cell types. In addition to facilitating the development of new therapies, this technology will provide scientists with a means of generating important cell lines that can be used for drug screening. Future elaborations of this technology should allow us to go beyond targeting genes to specific safe sites in the genome and allow us to freely exchange bad genes with good genes. We anticipate that this technology will be highly efficient and allow any individual patient's ESCs to be corrected at the genetic level.

Statement of Benefit to California:	Human embryonic stem cell (hESC) technologies hold the potential to revolutionize medicine, healthcare, and our understanding of human biology. Human embryonic stem cells hold vast potential for the treatment of disease and injury because they are pluripotent: these cells have the ability to develop into any of the more than 200 cell types in the human body. Scientists believe that hESCs can eventually be used to create therapies to treat previously untreatable injuries and diseases; certain chronic diseases may eventually be cured with a single administration of corrective cells. Devastating and currently incurable conditions such as AIDS, Alzheimer's, liver disease, diabetes, Parkinson's disease, muscular dystrophies, spinal cord injuries, inborn errors of metabolism, and many other diseases might be treated with gene-modified patient-specific, immunologically matched hESCs. In order to realize the full potential of ESC technology, researchers need to develop tools that allow them to safely introduce novel disease-fighting genes or to correct individual patient's genes in hESCs. At present, there is no safe and proven method to achieve this goal and thus a 'recombinase' technology must be developed. To achieve this significant goal, we will capitalize on our extensive experience in development of effective gene targeting technologies and with derivation and characterization of stem cell lines. We anticipate that our recombinase technology will make gene-corrected or gene-modified human embryonic stem cells as safe as possible for cell therapy and will speed the development of drugs that are safe and effective for all Californians, regardless of their ethnicity. This new technology and the new therapies that might result are expected to reduce the long-term healthcare costs to the State of California by providing cures to diseases and injuries that are currently chronic and/or untreatable. Support for the development of this new technology will ensure that California is a leader in embryonic stem cell technologies, making California better equipped not only to treat its own citizens but also to compete for the multi-billion dollar market that is expected to develop with advances in ESC technologies. Spurring industry, research, and product development in the biotechnology and healthcare fields will further benefit California by attracting highly skilled and well-educated individuals and tax revenues to the state.
